Remarks

In view of the following remarks, reconsideration of the outstanding office action is respectfully requested.

Alzheimer's Disease is a devastating illness affecting nearly 4 million Americans, costing the country billions of dollars in direct care, lost income, and – most importantly – costing untold anguish for millions of American families.

The disease symptoms start insidiously, with relatively non-specific signs and symptoms. Subtle memory loss, occasional word-finding difficulties, irritability and aggressiveness can all be signs of a disease process from a clinical perspective, that has already affected the brain substantially. Over the course of several years, the disease progresses to profound amnesia to the point where patients do not know themselves, or their family. Frequently, this amnesia is accompanied by frustration and paranoia. Ultimately, patients lose all ability to care for themselves – to dress themselves, to bathe, even to control their bowel and bladder. Their last years are frequently spent in a nursing home. As the average age of the population grows, the number of Alzheimer patients will explode because it is a strongly age-related illness.

While these clinical symptoms are going on, the changes in the brain are marked. By the time the very first clinical symptoms appear, there are innumerable microscopic deposits of a protein called amyloid ("A-beta" or "Aβ"), as well as changes in the brain cells themselves. As the disease progresses, the brain shrinks and loses as many as 50% of its cells.

Genetic risk factor analysis and molecular biology suggest strongly that it is the deposition of Aβ that is the critical aspect of this disease process. Seeing Aβ and neurofibrillary tangles in the brain under the microscope provides a definitive diagnosis to a neuropathologist. However, these changes are far too small (100 times too small) to be seen by even the most sophisticated clinical imaging devices such as computerized tomography or magnetic resonance imaging.

The ability to detect amyloid deposition and neurofibrillary changes in neurons *in vivo* would provide a definitive diagnostic test for Alzheimer's Disease. Moreover, the ability to visualize and quantitate these changes would provide a definitive means of tracking progression of disease and the effectiveness of potential therapeutics.

The present invention is directed to overcoming the deficiencies in the prior art by providing a method of diagnostically detecting and imaging Alzheimer's Disease and other neurodegenerative diseases.

The rejection of claims 1-34 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent Publication No. 2002/0115717 to Gervais et al. ("Gervais") in view of U.S. Patent No. 6,280,386 to Alfano et al. ("Alfano") is respectfully traversed.

Gervais relates to the use of amyloid-targeting imaging agents for imaging amyloid plaques *in vivo*. The amyloid-targeting imaging agents include an amyloid targeting moiety linked to a labeling moiety. The targeting moiety localizes the imaging agents to amyloid plaques, and the labeling moiety allows the imaging agents to be visualized by ultrasound imaging, computed tomography imaging, magnetic resonance imaging, nuclear medicine imaging, optical imaging, and elastography. Labeling moieties taught by Gervais for use in optical imaging include fluorescent or colored dyes. There is no suggestion in Gervais of using simultaneous multiphoton excitation, as claimed.

Alfano teaches an imaging system in which images of objects within tissue are enhanced by applying a contrast agent to a sample to be imaged, thereby forming a luminous object. The tissue is illuminated and 2 image signals are recorded. These 2 image signals are subtracted to minimize an image component resulting from the tissue and to enhance the image component resulting from the luminous object. Alfano also fails to suggest the use of simultaneous multiphoton excitation.

The use of simultaneous multiphoton excitation in accordance with the present invention has a number of very important benefits. In particular, multiphoton excitation has a very high resolution capability, on the order of one micrometer (page 20, lines 26-29 of the present application), and can reach unprecedented depths (page 27, lines 15-18 of the present application). In addition to permitting high resolution imaging of living tissue, multiphoton excitation has the unique advantage of incurring only minimal photodamage or toxicity on the living tissue being imaged (page 25, lines 25-26 of the present application). These unique features of multiphoton excitation imaging make possible the detection and observance of certain Alzheimer's Disease-like lesions that are otherwise undetectable with prior art imaging technologies (page 25, lines 21-25 and page 46, lines 11-12 of the present application). Multiphoton excitation methods of imaging also provide the opportunity to evaluate a relatively large 3-dimensional reconstruction of the cerebral vasculature (page 32, lines 17-19 of the present application). Additionally, multiphoton excitation of fluorophores

provides a method of imaging with improved background discrimination and reduces photobleaching of the fluorophores (page 12, line 19 to page 13, line 8 of the present application).

Since Gervais and Alfano fail to teach or suggest the use of simultaneous multiphoton excitation of brain tissue for detection of neurodegerative diseases, the rejection of claims 1-34 for obviousness over Gervais in view of Alfano is improper and should be withdrawn.

In view of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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